FOOD AND DRUG ADMINISTRATION

WORKSHOP ON PRECLINICAL TESTING FOR ENDOVASCULAR GRAFTS

THURSDAY, JULY 29, 2004

The workshop came to order at 9:00 a.m. in the Grand Ballroom of the Hilton Washington, DC North, 620 Perry Parkway, Gaithersburg, MD. Dorothy B. Abel presiding.

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9:08 a.m.

MS. ABEL: We'll do our usual formal introductions.

DR. CHUTER: Well, I was just going to leave this title as fatigue. Many of you were here last night. I thought I'd narrow this subject a bit and talk about the device.

Let's see where we go. All right. Okay. So there was a time when just about every stent graft that went in was destine to come out in pieces, and it was a very instructive time. There were examples. If you ever want to find an example of any form of failure of the stent graft, you just have to look at the old MinTec Vangard experience and there will be plenty of pictures with everything you want to know.

I'm just going to plug through examples of failure of every part of the stent graft and every part of the stent graft has failed at some time in some patient with some device. Then I'm going to go through some of the factors that

predispose towards failure. Obviously, a lot of the progress that we've made has been in identifying the failure modes, characterizing them, looking for the causes, finding out what works, what doesn't work and then doing a little bit of evolution to winnow out the solutions.

So here's fabric failure. And you can see this is a micrograph of fabric from a couple of pieces that have been subject to repetitive impact with an adjacent stent. This is what happens if the flat surface of the stent is impinging on the fabric. You get some fiber flattening, perhaps a little bit of a defect, but nothing like the horrendous defect that you get if the apex of the stent is impinging on the graft. And it's just the kind of recipe for disaster that you would imagine where you have this soft pliable object moving under hemodynamic forces against a far more resilient object. And the answer that most people have found to that particular problem is either to get more of the stents in between the orificial sealing and attachment stents, get rid those altogether, or to

strap the stents down so that the potential for movement between the fabric and the stents is eliminated. It's kind of like, you know, putting on seat belts. The problem is that the seat belts themselves can do some damage. And those, too, can hurt the fibers.

The underlying problem in the MinTec and Vangard experience was the malalignment of the stents that was caused by breakages of the sutures that held them together. But they're not the only ones where the sutures have broken. And if you look at the AneuRx explant data you'll see that suture breakages are very common. It's just that there's sufficient redundancy in that system that the suture breakages don't seem to have caused much of a problem.

One of the problems they do seem to have caused, at least early in the experience, is with a more loosely woven version of the fabric is to produce some suture hole leaks. The job of holding the stent to the fabric can also injure that fabric, as I said, and you don't always see a manifestation

of it like this where you have sort of a water sprinkler opening into the aneurysm. But what you do see if you compare the rates of shrinkage between a device like the AneuRex and some of the others as has been recorded, is a profound difference in the rates of aneurysm shrinkage. And you wonder what that represents.

The excluder, obviously, is something of a different phenomenon, perhaps on a more microscopic level. But you wonder what that represents in terms of sac pressures. Of course both of those fabrics are being replaced. And in light of the discussions that we had yesterday relating sac pressure to migration force, it will be interesting to see how those changes in fabric impact the migration rate of those particular devices. That's a very nice experiment that's going to be going on right now.

One of the big sources of fatigue failure with these devices has been in the skeletal elements either the stents or longitudinal struts, and all of the different materials have been prone

to breakage. But Nitinol in its early forms seems to have been particularly proned.

If you looked at the old Nitinol basic systems, the wires were black. And what that meant is that they were covered with oxide. And it meant that they hadn't been properly electropolished. And if you looked at these microscopically there were multiple surface defects which either became the focus for a stress strain propagation of fractures or you've got this kind of funky corrosive phenomenon going on, perhaps also aided and abetted by some of the repetitive stress and strain. So you can go from this to this with an improperly treated Nitinol wire.

And this, you would see fractures in all parts of this system, particularly susceptible elements in some of the systems just to call out a few examples of the longitudinal struts. These are in Talent, was particularly prone to breakage, especially if it was on the inside of the curve, longitudinal struts and the excluder. But not only Nitinol stents, the stents of the bifurcation of the

Zenith device, the original stents were fairly prone to breakage.

And of course barbs. The prototype of that was the barb fractures that we saw in the Yanker device. And really, those barbs were a very active securing mechanism. They were all that held that device in place. So that was a bit of a disaster for those. And the problem seems to have been a manufacturing one where the radius of curvature was just a little bit too tight on the butt.

These barbs are attached in a totally different way. They're passively deployed. They point down. There is no acute curvature but still they will come off.

The answer the Cook people seemed to have found is redundancy, just a multiplicity of these barbs. And if you look at one of the devices when you first implant it in an angulated neck, it's very easy to imagine how if you tilt this stent, let's say you tilt it that way, the aorta is angulated in the opposite direction, how you would

be loading up a couple of these. And, in fact, Bob Skelter is very big on this concept where implantation of this device into an angulated aorta is often accompanied by some sort of settling over the course of the next year or two as the load shifts and the device becomes reoriented and spreads that load out.

These sutures were also the site of breakage, probably as much as anything evidenced by the fact that the stent was doing something to keep the device in place. Because once all those sutures fractured, then the remainder of the device would migrate distally. The answer to that, of course, again was redundancy; more sutures.

And that's probably a pretty good example of the kind of testing that we were talking about yesterday where, you know, you have a basis for comparison in the old device, you can see how it relates to the new device and you can extrapolate that into a change in clinical performance.

So what is hurting these devices? It's

not steady state forces, the kind of things that have been in models and measured, and used to do device testing. You know, it's pulsatile forces. It's this kind of little dance that goes on time and time again through the life of the device.

And we followed a bunch of these devices at various stages from implantation through about 4½ years. And you can see some very interesting changes going on.

As you look at the device the Bedford is most prone to movement at all. There's two kinds of movement. There's the translational movement where the things moves up and down and from side to side, and then there's a pulsatile movement where it changes its diameter.

I don't know if we could get the room lights down a bit so you can see this, because it's quite subtle. Could that be possible? See, it's magnified as much as I can.

If you look at the pulsatile expansion contraction of this graft, when you first put these devices in, the bit inside the aneurysm is pulsating

the most. You'll see that wall flopping back and forth, back and forth. And you put your hand on the patient's belly and it's easy to understand why there's a massive pulse there because everything is moving. You can see here everything is moving.

This patient actually is a little longer than that, I think it's a month or six months out, and that is all quieting down. This is the location of the stent that used to fracture. There used to be one stent there and when you fluor the examples, I've done a couple of those, you can see this stent really is taking the heat right at the bifurcation. Less so now that there are two.

But if you look at this segment now, we're a month or six months out, the pulsatile aspect of this, the in and out, has disappeared. Why would that be the case? Well, I think it relates to the pressure environment of the aneurysm, and I think we're going to find more and more that that's a very important factor in the durability of these stent grafts is the behavior of the sac and the pressure differentials between inside and

outside.

If you imagine a situation where -- if you measure these pressures, they don't have much of a pulse pressure unless you got a Fran type 1 or type 3 endoleak. The pulse pressure inside there, it's fairly flat wave form. If that is above diastolic pressure, you're going to have a phase in the cardiac cycle where the pressure is bigger on the outside than it is on the inside. And as it cycles through there, you're going to have this flapping back and forth. So systolally that's going to got and distally it's going to come back. Now, it's not going to move that much, because obviously those pressure changes in the sac would be abolished by any movement that they can generate in that graft wall. That's the sort of the capacities chamber for this whole thing.

And I suspect that's why these early stent grafts are flapping around, because clinically you put your hand on the patient's belly you will see a corresponding decline in the pulse of the aneurysm with a decline in the movement of that

stent graft. So that disappears first.

The next one to disappear is here. If you look at this neck very carefully, let's say you look up there, you'll see that there's pulsatile movement of this. It's somewhat obscured by the translational movement, but it is going in and out. And that is because compare the diameters here and here. This is partially constrained. It can go in and out. Obviously, it has the additional problem of it's facing -- it's compliance at the stent graft added to the -- well, it's compliance with the stent graft aorta component there is what is influencing the movement, but obviously there's some potential for movement because it's not fully expanded.

When you look at here, there's no graft, this one can move quite freely.

You follow these, this one is the next to go. So this disappears first, then this disappears. And the reason is this: Just about all of these stent grafts start out looking like a bottle, sometimes even more so than that. And we followed a lot of these patients just on serial x-

rays comparing the diameter here to the diameter here, which I call the oversizing index. And it's sometimes shocking when I look at my numbers of how I calculated the stent graft to find how much these things were oversized. Because is the unconstrained diameter and this is the constrained diameter. Well, you'll see over time this is eliminated, and it actually happens fairly quickly. By four years these all look at like Coke cans. They're as straight as can be. They are completely fully dilated. And if you plop them out, you'll see that the diameter rises and rises, and the gradient seems to be fairly constant and then it just hits a plateau. And where they hit the plateau; sometimes they'll get to one-to-one. It's usually in the sort of .9 to 1 ratio between this diameter and this diameter, or this and this.

So there's not necessarily full expansion, and I'm not entirely clear why, but something in that stent graft is stopping the further dilatation. Well, whatever it is, it's also stops the pulsation. These things stop pulsating

once they get to look like that.

This, of course, is unconstrained. It continues to pulsate.

And then what you end up this guy is four years out. I apologize for the graininess, but he weighs about 350 pounds. You've just got a straight sided tube here. This thing is completely dilated, there's no longer any pulse there. There's not been any pulse there for a long time. And the blood comes rushing straight down, impinges on the bifurcation and this is the kind of movement that it generates. And if you look at the changes in translational movement over time, they don't go away. In fact, there's a trend towards them increasing with time. And probably the increase relates to the increase in diameter of the inlet. Those of you who model the forces on here will know that that inlet diameter is a fairly strong component in influencing the force on the stent graft.

If you look down here these stent grafts are implanted pretty close to the iliac bifurcation,

which is a fairly fixed point in the arterial tree. You've got the internal iliac coming off there, it carries probably about here. It doesn't move very much. This is moving a lot, this is moving not very much. You can see what it's doing to that limb there. And the only thing that gives me any comfort there is that that limb is sitting inside the iliac artery because I can see those sutures fairly quickly wearing their way through the fabric.

So this is how we made the measurement. From those seni-loops we would generate systolic and diastolic images just from the extremes of the range of movement, and we would plot the positions of certain points on the stent graft and obtain estimates of the translational movement and also the pulsatile in terms of a percentage diameter change. So you can see down here the pulsatile movement is pretty much gone, the translational movement is really quite striking.

And you just go back to some of the analyses that have been done. You'll hear more about them later. And the force is determined by the

diameter up at the top there, the pressure, the angle and I think sac pressure because I think what we're looking at here is the difference between the two.

Interestingly, if you look at the migration rates, obviously this was not a pulsatile analysis, but it correlated pretty well with the findings from the Urista database in terms of mitigation risk. Same factors: diameter pressure, angle and interestingly type 2 endoleak seemed to provide some protection against rupture and I suspect that it's providing protection by the same mechanism, sac pressure force, migration rights. Migration being the primary predictor of rupture.

So how can we look into the forces a little bit more? Well, what we've been doing is taking CT scans from these people, segmenting them out and doing some computational flow dynamics on these. Go back to that one. And we can compare them with the fluoroscopic movements. It doesn't seem we can compare them in real time. But believe me, they both move.

This is just flow, but it's relatively easy to map out both temporally and spacially surface pressure, surface sheer, other factors in the generation force, although pressure of course predominates in all of that, and compare them with the movements of the stent graft, the corresponding movements of the stent graft. And interestingly, you can do the same kind of analysis where you're looking at flow and compare it to the CT scans and you'll find that these points in recirculation tend to end up as points in mirror thrombosis. There is correlation between this. What we haven't done yet is take that lumenal profile and model that and see if the formation of the thrombus has eliminated the eddies and the spaces and so on that where generating a thrombus.

So, to conclude, the pulsatile diameter changes by location and time from implantation. The bit in the aneurysm pulsates the most, but that doesn't last very long. The bit in the neck seems to pulsate probably for a couple of years, depending upon the degree of oversizing and how long that

oversizing persists, and then the pulsation of the top stent just seems to go on forever.

Translational movement varies by location in that the aortic elements seem to have more movement than the more distal elements. But it doesn't change with time. In fact, it seems to increase if anything.

The only consequence that we could find in these analyses of oversizing is that it perhaps correlates with the extent of neck dilatation, and we're not the first people to notice that. And by that the mechanism may be increasing the hemodynamic forces because there is some relationship between neck dilatation and migration risk. And it seems that based upon the temporal mapping of these forces that they are primarily acting on the bifurcation, which may become an issue for stent graft redesigns, and I think perhaps accounts for some of the astonishingly low rates of renal loss in the fenestrated experience. With the fenestrated Zenith where they're using a two component device. One device is attached to the aorta and doesn't seem to

move at all, and the other device is -- the other part of that device is the bifurcation and that's the bit that's getting all the heat. And it seems that that sort of separation between the two components functional and mechanical seems to have some beneficial effects in terms of proximal migration.

Thank you.

MS. ABEL: Well now I don't know what to call Lou's talk, because that was pretty scientific. You've got a challenge.

DR. SMITH: Well, thanks. Thanks, Dr. Chuter. I hope I do justice in following you, but I wanted to talk about the scientific perspective, the device integrity, fatigue and durability. And really it's all about how do you test for all of the stuff that Dr. Chuter just talked about.

There is some testing in the ISO, I wanted to just kind of go over that briefly. There is characteristics in there that are addressed in the testing, and then there are some limitations and some other special considerations.

This is the lists of tests that you see in the section of ISO 25539. The ones I've highlighted in yellow are the ones the workshop folks were asked to respond to, but there are several others. And I just wanted to point out that they're very interactive; you know, the strength of the material, the corrosion, factory and anastomosis strength is very similar to the strength of stent and attachment systems in the graft. You know, we've talked about that a little bit. A lot of these things are interactive, so no one test -- my point here is no one test covers everything. And I think that's really important.

So I just want to jump into the big ones. Fatigue testing. Obviously, Dr. Chuter showed us the kind of forces in motion and movement that we can see. There's a lot of failure modes that can be identified by fatigue testing. Primarily everyone's doing it to look at whether their stent is going to fracture due to pulsatile motion. But there's a lot of other stuff that goes on in vivo and that we're trying to replicate on the bench,

especially when the stents detached from fabric where there's tearing or wearing of the fabric and abrasion between overlapping components.

Typical fatigue tester. Just wanted to have one up there in case folks don't know what they look like.

There's a lot of types of fatigue testing. In the standard we addressed pulsatile fatigue, but there's also you know attachment method fatigue; whether you're using anchors or barbs or hooks, or whatever, and that could be a separate fatigue test that could be done.

There is wear and migration. Often in pulsatile fatigue testing we will generate forces that are worse case in terms of pulsatility, but those aren't always the worst case situation for overlap component movement or abrasion or wear. So you may have to do the test more than once. You may have to do it at a highly oversized condition or then maybe at a low oversized condition.

There's bending going on. You saw some of that. And there are other compressive forces. You

saw Dr. Chuter's translational movement up and down. That causes comprehension in some cases.

This is just an equation that's been rearranged a little bit, but it's out of the ISO. It talks about diametric deflection. It basically speaks to how you can calculate that based on compliance, percent compliance. And pulse pressure you might see, the delta p. And it's a very important thing to familiarize yourself with if you're going to set up a pulsatile fatigue test.

I want to jump right into all the other things. Corrosion. Versions 1 we saw some pictures there. There are several types of corrosion that the standard addresses. There's pitting corrosion, galvanic corrosion, crevice corrosion. We can keep going on with the list.

The examples that were shown are mostly a surface finish issue and it can create pitting. Galvanic, obviously, dissimilar metals. If you have gold markers in touch with your stent material, something you need to be concerned about.

And crevice corrosion where you get a

micro-environment being created, say, underneath sutures or underneath bonding tape and how that's going to effect your metallic components.

This is just a typical result of ASTM F2129 where it's a potential dynamic curve. You can see current density as a function of the potential placed upon the sample. And these are like the typical curves that you should be used to seeing.

Obviously, Dr. Chuter kind of showed you the MinTec example, but corrosion can lead to the picture here where you really should be looking at devices after explant that look like the picture on the other side of the screen, depending which way you're facing.

In all of this, of course we're looking at stresses and strains trying to determine what are the loads. In the standard it talks about calculating loads due to manufacturing, deployment and in vivo conditions not just the in vivo conditions. And what in vivo conditions are we talking about? We can talk about pulsatile pressure and flow, that's what we have been talking about.

There's also bending and translational motion. And all of these analyses can be used to feed into how you're going to do your durability testing; whether it's just a diameter kind of test in a pulsatile fatigue testing or bending, or whatever.

Obviously, the strength of how your stent is attached to the graft is important. Failure modes that are evaluated by this kind of testing are pretty obvious, material tears or sutures breaks. Basically the separation of the two components which leads to many of the issues we've seen.

There's standard characteristics that have not been addressed in our testing, and that's probably the primary reason why we're all here to see, you know, about changes in the shape and diameters, tortuosity, disease vessels and angulation.

Tortuosity and angulation. That's seems to be our mantra this weekend. I think it's real important, it leads to bending, it leads to a whole bunch of other forces. I do have a video here. It's

not as good as Dr. Chuter's. But, you know as it runs you'll see the motion. This is mostly the thoracic aorta, but you can see that motion being translated down into the abdomen and it continue. If you just focus on these bends. I guess you can't see it. That's good for me. So we'll just stop that little work.

But you can do fatigue testing out of the pulsatile machine where you can see here we've got some samples set up to be bent and moved and under bending fatigue versus just your normal pulsatile fatigue. Tortuosity and angulation leads to this kind of motion. There's no way to get around it and Dr. Chuter had some eloquent video that I couldn't reproduce.

So, again, we got the same old monster here. Limits of our testing are, you know, trying to incorporate tortuosity, neck angulation, changes after you implant. All these things are very difficult to reproduce in testing.

A lot of the limitations are based on what we've learned. It's difficult to put everything

into one test. I think we're getting better and better at defining the clinical forces and what tests to put together to at least study those, but it's common sense after a while that it's not really possible to assimilate all the known forces, at least in one test. Trying to do flexing and bending is difficult while you're also trying to do pulsatile motion on the stent.

Of course, we've talked about the other things, calcification and thrombus, changes in the sac and the differential pressure across the wall. All of these change, you know, effect the way we want to determine our durability testing.

To try to determine worse case, engineers are always looking at worst case. You know, worst case delta p is where the sac pressure is zero and these kinds of things to set up a test that subjects devices to what they would consider to be some of the worst conditions that they're going to see in the clinic.

And I just wanted to touch real briefly on special considerations for extenders and cuffs

and stuff like that. It's not possible, necessarily, to put all your components into the same test. And like I said earlier, you may really have to do different types of testing. Setting up a fatigue test to understand how many times your stent is going to fracture under just basic pulsatile motion is a different game when you start overlapping extenders or cuffs, or whatever you want to call them.

At different oversizing conditions there's different kind of abrasion that occurs. In some conditions no abrasion can occur. But in the same two devices together in another condition you can get wear and abrasion and fabric pulls and what have you.

When someone throws a Palmaz stent in on top of a Nitinol stent or whatever, you could have issue with galvanic corrosion. It hasn't really shown up that much, but it's a potential that needs to be examined.

Basically, in conclusion, there's guidance for these things. If you look at the ISO

standards it not only in and of itself is a guidance, but it points to a lot of other guidance documents, whether they're ASTM methods or ISO methods. And it's really an ongoing process. There's never going to be one document that a manufacturer can pick up and say this is all I have to do. A manufacturer has really got to look at their design, look at the target that they're going for in terms of the clinical use and you may have to come up with an array of tests. I mean, there may be 30 tests in that standard, or 34, or whatever the number is but coming into submission, you've probably got 50 different tests that you've performed. So it's really not, you know, one durability test or one fatigue test or one material test that can cover everything.

Thanks.

MS. ABEL: We have a special guest speaker.

PARTICIPANT (Cook, Inc.): I'd like to introduce Kurt, who I work with. Kurt works with CSIRO, which is an Australian research organization.

And we had a grant from the government, a bit like your NIH grant because we wanted to look at the effect of pulsatile flow. So we pulled a pulsatile rig to see how these things work. And our concern was how we build things inside an aneurysm. So the simplest is the connection of the short leg. But if we go for fenestration like Tim mentioned, we separate the top from the bottom to separate the forces out, but also to separate out the orientation.

And when we come to the thoracic we don't have that bifurcation situation at the bottom, but we have a lot of force on the curve of the arch. So now it's a different force mechanism that tends to separate the modules. And the reason for having modules is it's very hard to get a length assessment. So to get a proper length assessment use the trombone principle. And most of the times people will underestimate the length.

So we wanted to know what was the stable position of two pieces on a curve or what was the force that was going to drive these things apart.

So we built the pulsatile module, the pulsatiler, a flow situation which wasn't that easy to do in the beginning.

We acquired an artificial heart to discover that the artificial heart really doesn't produce anything like the forces and pressures that we need. So Kurt had to build a pressure pump. So I just want to show you that and the effect.

And it's interesting that you always think you're going to solve it and you find someone else has worked it all out before you get there. And So Tim's worked this out, and we discussed it yesterday, and we have the new term that Lou said was a differential pressure. And we thought of pressure differential. So we really ought to use that term from the inside of the systolic to the sac.

And we found that the movement was quite a lot, as Tim did, and especially in the model where all the pressures are equal because he explained it: You have a pulsatile pressure inside.

And then when the pressure differential

is such that it's great enough so the graft in fact inflexs and it can come apart at that stage, but the movement ceases.

And the point there is that if you look on the -- now we can study this. If you look at it you find that it's working all the time. So when it's moving it's working. And that's a real fatiguing motion.

It also I think -- I'd like to put forward the concept that while we have to have tests for many different things, we can set up the condition and we can say well if there's only one test, is it going to work in a patient? So we set up the worst scenario. So we say, okay, now 10 centimeter thoracic aneurysm on the arch with a pressure differential of this, and we set what we ought to be, let's put it in there and see you meet the standard.

So we'll see if our video flows. Give it to Kurt.

MR. LIFFMAN: Right. I'd like to not take too much time because I know time of the

essence.

When I first started talking to Michael or working with Michael -- Michael you'll have to come back here, you know. But we're looking at forces on grafts. And so Michael asked me to work out the equations for that, which we did and we published a number of years ago. And as Michael said, we want to -- we went through quite a few machinations to produce the pulsatile flow rig, and this is our current evolution. It's basically -- I don't have it with me. But basically it's a computer controlled unit and we can dial in any particular pulsatile profile that we'd like.

Our motor is -- the pump is over there. And you just basically put in your wave form and you're fine. But we had problems with the pressure and so -- because when you put in a motor which can generate any wave form that you like, you still have to worry how pressure propagates through the system. And so we had to put a damper in. It's called a windkessel. It's that device over there. And so the pressure wave forms still nearly could work.

We want to measure the forces on the grafts. Thank you very much. That's exactly what I need.

So we want to work out the pressures on the grafts. And this is our main units over here. And what we constructed was a system like this. This is an acrylic model of a symmetric bifurcated graft. We have a load cell, which is connected up to a computer. We just measure the deflections of the wave, the load cell and that gets translated into voltages which can then be translated into pressures by calibration.

And we have flexible rubber membranes just from rubber gloves. So attached you got pressurized fluid, in this case water or water glycerine mixture going through here. And we can measure with a pulsatile motion what the forces should be.

So the first case we looked at was the steady state flow case. I haven't got the equations here, but when I first arrived at them and published them, there was some concern and still is some

concern in the medical community that we developed equations which are for steady state, that is continuous flow. But of course in the body it is pulsatile flow and so then people are saying well how realistic is this?

Well, first of all we looked at the steady state flow. And the dots here, the measured forces and the line here basically is from our equation. This is assuming the initial -- in the inlet diameter of the actual acrylic graft that I showed you before, but when you actually pressurize the system this joint goes out about a millimeter, it expands. And so when you put that in, that expansion in, you get a pretty good fit between theory and what you measure.

So in this case we've validated the pressure flow or the force flow equations that we derived. But then we had to look at the pulsatile flow equation. And when you start going to pulsatile flow you get into quite complex mathematics. And so I tried to simplify it as much as possible by using a standard momentum equation,

which were shown yesterday.

And so I took the bifurcated symmetric graft and just looked at a pressure wave propagating through the system. And you have this symmetric graft. We have a body about -- LB is the length there and you have the legs. And they're all at an angle, alpha is the half angle. And when you go through and see, I don't know if you want to see, but here's the restraining force and here's what you get to the steady state flow. If you just had continuous steady state flow you get out this equation. And as was shown yesterday, the dominate term is this entrance term when you have the pressure in the area. That's what really determines the forces on the graft, because all the other terms tend to be quite small. But when you put in pulsatile flow and you start looking at it, you get this extra term. And this is the density here of your fluid. In this case it's going to be close to water. And then you have actually the length of the graft becomes important. All right.

So when you start worrying about

pulsatile forces in this very simple approximation, the length of the graft starts to become important and also the flow rate. This is the flow rate. So this is the pressure as the flow is a function of time.

But it turns it out that this term can be neglected. It's very small. It's about the one percent level compared to this term. So you're when you're looking pulsatile flow, at least in this theoretical sense, the steady state flow equation which people have been so concerned, is actually the appropriate one.

And these are some forces or PSB from our initial experiments.

So these are experiments we've done. Here is the pulse time just in one second. And this is what we get from the experiment from our load cell. This is a bit of hysteresis and time lag in our load cell. And this is what we get from our pressure equation.

Just basically by looking at this particular terms. You could even neglect most of

these and just look for P times A. And you get a moderately good fit. We're trying to improve the fit. So -- but that's basically where we are at the moment with that, and we're doing some more experiments.

Okay. Stability of modular grafts is what Michael was talking about. Michael is very concerned with modular graft system, about how they're coming apart and what sort of pressures. And we're still doing some ongoing work on that.

And we have our flow rate. Basically this is our aneurysm. It's made out of acrylic and we put in two modular grafts. And we have the systemic pressure going through here. Typically we go 130 on 80, pulsatile time of one second or so. And we can change the pressure inside the aneurysm. So we can look at how the behavior -- we can put the grafts at different angles, different overlaps. So there's some variability in the system but we can tighten all the variables and so we can make sure everything is consistent.

And this gives you an idea of the

movement that Michael is talking about. When you have a main pressure difference, and I'll get him to come up here soon and discuss that, but when you have a main pressure difference of zero between the graft -- here two grafts are basically joined together. And we call two stents -- this is our stent, unit of weight stint. So we have two stent overlap. I think hopefully most people understands what that means.

And there's a pressure difference of zero between the aneurysm and the systemic pressure. You get this movement. This shows -- this redline shows the diastolic and when it's on systolic it's up here. So it's going backwards and forwards.

When you have a pressure difference which is equal to the pulse pressure, maybe you've got 130 on 80, so the pulse pressure is 50 mil, everything gets pressurized. So when the main pressure difference is there, it just becomes tightened up and it has actual structure and it stops pulsating.

So hopefully this will work. WE shall

see and keep our figures crossed. It doesn't come up.

MS. ABEL: All of you have to gather around the laptop.

PARTICIPANT: Copy off that computer, and just put it on the video.

MR. LIFFMAN: Sorry. Trouble with the computer. I don't understand. Function F7.

You can come up later on and have a movie. That's fine.

All right. But anyway, this is on the side view. It's the same sort of thing. You get this pulsatile system and there's zero millimeters difference. And when it's fully pressurized, you get the idea. Otherwise it's just pulsating backwards and forwards and you can see the movement between the stent systems. And same sort of thing over here as well.

Okay. And that's the end of the presentation.

PARTICIPANT (Cook, Inc.): You got bitten by the technology a little bit. Need a bit

of preclinical testing there, I think.

What the video showed was that the graft did come apart. And one stent overlap was very unstable. And at two stents -- two stents overlap it would part would you got to the pulse pressure. And you needed three stents overlap to sustain a pulse -- a pressure differential of 50 millimeters. So that transcribes to IFUs and a testing situation. You know that if you haven't got at least two stents overlap than you have a situation where it could come apart.

It won't always come apart and people will say in a clinical situation how come it doesn't come apart? It won't come apart if it gets to the wall before it comes apart. So that's why in a big aneurysm it's more likely to come apart in a smaller aneurysm because of the distance of travel. So the reason for having a long overlap if you are using modular grafts that can move is to allow for a certain amount of travel as well.

MR. CARDELLA: While they're setting that up, can I ask a question again? When you say

the pressure difference is zero --

PARTICIPANT (Cook, Inc.): Well, you can just see it moving. This is when the systemic pressure inside is the same as outside. And this is when the pulse -- when it's down to 18, the pressure differential is 18. So the pressure differential is 18 and there's still some movement. And then it goes up to 50 and it's essentially fully inflated, and that's why you don't see the movement.

If we go back and you watch the join -- will it go back? But if you watch this part here when it goes around again, you see here. You can see this is actually working. So you just wonder sometimes whether you start to get a leak if you don't get a proper seal.

MR. CARDELLA: So a question again, in the upper left hand panel before you take that down, when you say the pressure difference is zero does that mean that you are helping 51 millimeters of pressure inside the graft and 51 millimeters of pressure in the sac chamber in that aneurysm sac chamber. That would be the difference of zero.

That looks to me like you'd have a high pressure inside the graft and zero outside the graft. So it's not a pressure difference. You're just saying the pressure in the sac on this picture -- well now on this picture. The pressure is the sac is 18.

COOK, INC. The pressure -- the pressure differential was zero between the systolic and the pressure in the sac in the first one. The pressure differential here is the pressure differential between the systolic inside and the pressure in the sac. And what Tim said there was very little pulse pressure within the sac. So we have a -- and may have a pressure differential between systolic and the pressure in the sac of 50. And it's essentially inflated because it's above diastolic. The pressure differential is above the pulse pressure. Pressure differential is above the pulse pressure it's stabilized.

MR. ELLER: Just a question here. Was the stent graft sealed in this experiment?

MR. LIFFMAN: No, they weren't sealed. We just put them el natural and we just had water

going through here. So there is some leakage going through the grafts. We just wanted to make sure we didn't interfere with the friction and we just had water and maybe next time we'll put glycerol and that apparently stops leakage.

PARTICIPANT (Cook, Inc.): It seems the same question because you have outflow from the bottom. So there's differences, and like if you have a lot of outflow form the bottom, a little outflow through the graft, you've still got outflow. So it's really the -- it's the pressure differentials that matter.

MR. LIFFMAN: So Michael, what was the pulse pressure on the inside?

PARTICIPANT (Cook, Inc.): It's 130 to 80. So as someone mentioned, maybe that's a bit low. If we're going to test, maybe we should test when someone's running upstairs or something and their blood pressure is 220 or something like that so we can have a pulse pressure of 200 on 100, which gives a pulse pressure of 100. And as Michael said yesterday, maybe we should test for a pressure

differential of a 100.

DR. CHUTER: Could I just ask Kurt a question?

Kurt, you said that the -- when you ran the equation with the pulsatile flow that the pulsatile element really was quite trivial compared to the pressure elements. Did you run the equations with pulsatile pressure as opposed to pulsatile flow?

MR. LIFFMAN: What I'm talking about when I'm saying pulsatile flows is I mean the flow and the pressure. So the steady state flow equations you can also just -- the pressure can be a function of time. So it can be pulsatile as well.

DR. CHUTER: I see.

MR. LIFFMAN: All I'm saying is that when you look at the equation that's been shown yesterday, the momentum equation fits into two terms. One it's pressure time dependent, it's a volume integral. And the other one is a surface integral. But the one with the steady state flow is a surface effect,t he surface forces that we're

looking at. And that's where the pressure and the area comes in. When you worry about the volume and the time part, that's what we're looking at in that extra bit of that equation. That's where that pulsatile flow comes in, the flow through the graft. It turns out it's very small.

If that term were to be of the same magnitude as the pressure area term, you'd need a pulse rate of 100 times per second. That's how small it is. And as a pulse rate is about one per second, you can basically neglect.

And so the steady state force equations that we've been using appear to be okay, at least for the approximation we've looked at for if you just make the pressure change with time.

DR. CHUTER: All right. I'm still puzzled. Let me ask you another question.

MR. LIFFMAN: Okay.

DR. CHUTER: Okay. If you neglect the flow related effects is there a temporal change in the pressure related effect according to the pressure at that particular instance? So, as the

pressure varies through the cardiac cycle, does the force vary through the cardiac cycle?

MR. LIFFMAN: Yes, it does. It's directly proportionate.

DR. CHUTER: So there is pulsatile variation in the force, it's just that the flow related element of that is small?

MR. LIFFMAN: That's right.

DR. CHUTER: Okay.

PARTICIPANT (Cook, Inc.): There were a couple of things on that -- on a chemical side if you -- if you do a fluoroscopy and you see your graft is moving, then you suspect you have a significant endoleak just by inference.

And the second thing is that very early on we put a spine along the graft. And we took it out for -- I can't remember the exact reasons. But I just wonder whether -- the reason I never understood proximal migration at the top end was because there is a certain amount of -- continuing there. And if you don't allow it to do that, maybe you can push it upwards. I'm not sure about that.

So maybe the rigidity of the graft is a factor.

MR. SMITH: I have a question for Kurt as well. You know, you're putting this graft into an acrylic tube or an acrylic aneurysm. How much of that do you think dampens the effect of what's going on? Is there any issue with wave reflection and things that we're not considering here?

PARTICIPANT (Cook, Inc.): There may be a very important issue with wave reflection. In all the analysis I've done I haven't looked at the reflection of waves. And what you can have happen in the graft is you can have the waves interacting such they either reenforce or they negate. And so you might have greater pressure differentials.

The way I've tried to look at the problem is I go step from step. And so we do something simple first, do steady state flow. The next one is well we don't worry about the pressure waves. Let's just look at the momentum equation, look at this extra time then in turn. And then the next one is going we worry about the pressure waves. And there's sure to be important facts there, in

particular with restenosis probably, you know, at the ends of the graft. Because the graft's structure is different from the artery and you've got all of this sudden change within the artery. So there are going to be pressure changes there, so that's definitely going to effect the environment of the artery, so it would be important.

DR. CHUTER: I got another question for Kurt. As you got this thing pulsating and it's dilating and contracting as it goes through the cardiac cycle, obviously that's driving fluid in and out of the space around the graft. Presumably your pressure control mechanisms were capable of eliminating the pressure variations that that would have put on that space --

MR. LIFFMAN: No, but it's an important question because what's going to happen is the graft expands and contracts, it's going to change the pressure within the sac.

DR. CHUTER: Exactly.

MR. LIFFMAN: But all our analyses assumes a rigid tube. I mean, that's standard

analyses. That's an approximation. So the next step is also we have to look at the -- in the graft. And that will change the pressure in the sac, as you're explaining. If the graft were perfect like a concrete tube, there'd be no pressure transfer into the sac.

DR. CHUTER: Right. But it's not.

MR. LIFFMAN: But because it expands it contracts, that's where you get the pressure transfer.

DR. CHUTER: Were you controlling the pressure in the sac or the volume in the sac, though?

MR. LIFFMAN: In the sac we were controlling the pressure. We just had its --

DR. CHUTER: So it was an infinitely compliant chamber?

MR. LIFFMAN: Basically, yes.

DR. CHUTER: Okay. So if you were to mess the compliance of that chamber, i.e., the way that pressure and volume were related in that chamber, you could probably try to mimic the

compliance of an aneurysm, and that would give you a closer approximation to sustain --

MR. LIFFMAN: Absolutely correct. So one of the next things we're going to do is the latex aneurysm if we can get the funding. Hint. Hint. We're going to do a latex aneurysm and just measure everything in there.

You're absolutely right. Again, it's the first approximation.

DR. CHUTER: Okay.

DR. FILLINGER: If you have -- in your aneurysm sac though, in a sense you've got -- I mean you have a place for that fluid to go when it expands, so it's really not very dissimilar to what you're already doing unless, of course, you have the instance where all of them are thrombosed. But that's not that common.

MR. LIFFMAN: You're very kind. But in your particular case that you're talking about, you don't guarantee that the pressure in the sac is always the same. We've sort of guaranteed that the main pressure is always the same.

MS. ABEL: Very well. I think we better move on and start talking about the other things we have on the side.

I think there are very good presentations this morning that really helped to demonstrate that this is a very complex situation that we're trying to deal with in terms of all the forces that are actually on the grafts.

I just went to mention a couple of things with respect to the compiled work assignment. I keep losing my point. Sorry.

In this side I just wanted to point out, again we really can't calculate any two compile rates based on the information that we provided. But it is interesting to see that people who did observations with respect to loss of graft integrity or suture integrity where anywhere from 1 to 27.9 percent. So there are some devices that have had some pretty significant issues with respect to these things.

And also if you look at the identified fractures, and these are from the clinical studies

that people reported to us, here I think it's interesting to see when they happened. It looks like most of what's going on is between 3 and 12 months, which gives credence to FDA's requiring a 12 month data. At least we're capturing that information within our clinical studies.

We also asked people to tell us about their explant analyses, and we had a total of 329 explants reported. In this table it's a bit busy, but again if you just look at kind of the grouping of where most of the observations occurred for an awful lot of stent fractures are occurring in the 12 to 30 month time frame -- now we can't be sure that that isn't going to continue in terms of those numbers because we don't know the number of patients at risk farther out. But there's a pretty significant number of factors that have been identified. And this is there were five respondents that had observations of fractures and only two that said that they didn't have any at all. And it's interesting, too, to see that the hooks and barbs only have one case identified.

And so, you know, this obviously isn't totally reflective of what we know is happening in the clinic, but this from the explants.

The additional explant observations we've got graft material there. Again, five people with observations, two don't. And a lot of that is going on in the 12 to 30 months time frame.

So I'm not going to spend any time to talk about the information that people sent back to us because I think we've got a good basis based on the prior presentations. Yes. So I think we'd be best to not break yet but go on to the slides that we want to be discussing.

MS. SMITH: And I think, like yesterday, we want to look at whether the -- that have been seen and that were identified by respondent can actually be evaluated in a fatigue and variability test. And the other thing that we wanted to evaluate was if there are things that are seen in the testing but not in clinical use and can be defined as testing artifacts.

MS. ABEL: So ISO says we're looking for

stent fractures and most people who responded said they did, but not everyone which was kind of interesting. Because I would assume that the focus of a fatigue durability test would be to look at device integrity. Would everyone agree? The answer should be yes.

And we wanted to talk briefly about what you do in terms of testing artifacts. And we have a lot of books, quite honestly, who say we always saw these things falling apart but it's because the testing is too severe or, you know, it's worst case, etcetera, etcetera. So how likely is it truly that you're developing a test that is so rigorous that if you see a stent fracture that it wouldn't be a realistic observation? You now, if you think you would see fractures in your bench test in your fatigue test and that would not be an indicator or potential to see that in the clinic?

MR. VASUTEK: Well, you test to destruction. Surely you're going to push, so you're going to see failures but a higher level of compliance or whatever than you would expect to see

in vivo.

MS. ABEL: So I think that's a very good point. You know, I think most of the testing that's been done so far hasn't been necessarily, you know, to destruction hasn't been to failure. It's been, you know, trying to simulate reality. And, obviously, we're not very good at that right now. But even in an attempt to simulate reality would you expect to see failures or be able to explain them away?

MR. VASUTEK: Well, if you're simulating reality, then you would not expect to see failures.

MS. ABEL: But you're attempting to simulate.

MR. VASUTEK: Okay. If you're attempting to simulate, you wouldn't see failures. But if you're taking it beyond what you think is reality, then you would expect to see failures. So for example, if we try and simulate in bench testing or screening, we've doubled the loads when we get a failure in half the time or if we double the motion from the testing, will we get a failure in half the

time as well.

So when we use, I guess, conditions that are accelerative, then we produce failures in a relatively short period of time. Are they clinically relevant and how do we interpret those?

DR. WHITE: There's a problem with that accelerated testing which is probably hierarchy, but I mean the 10 ten cycles and accelerated are for straight segment stent tests and it's not predicted to failures which have been at angles or transition zones clinically. So my observation would be is that accelerated testing would give you artifacts if you do get it in a straight model, and it ought to physiologic in the angles if you're trying to predict the event.

MS. ABEL: Dan, did you have something you wanted to say?

MR. CHWIRUT: Yes. I think there's two items that you can look at in trying to determine if the failure in the bench test in artifactual. One is where it occurs and second is when it occurs. Obviously, if you put something in, put it on test

and then the first, you know, simulated six months or something like that something breaks, probably something was a amiss. It was deployed improperly, the device was not representative of clinical quality or something like that.

The other thing is you look at the comparison between your analysis and your test. And if you've done an FEA or some other stress analysis of the test conditions that you're trying to produce, and you're getting failures that are totally at odds with what your analysis tells you, again something is amiss and you might look at that failure as being artifactual.

MS. ABEL: Thank you.

Okay. We can move on to the failure mode state, graft fatigue. Have not shown what the difference is between fatigue and fracture other than maybe it just gets tired, it doesn't break all the way. So we're just going to kind of say -- yes, more people actually looked at fatigue an fracture.

Well, that's actually separate. The fabric we look at separately. This is with respect

to the stent, but maybe that's what people -- maybe they grouped it together.

Barb and hook fractures, are these --you know, again, just the straight durability tests that we're talking about described in the ISO standard. Is this test really something that you can use to evaluate barb or hook fractures or is that a separate test that you need to design?

PARTICIPANT: Are you talking about just a radial fatigue test or are you talking about longitudinal fatigue or multiple possibilities? This table is geared just towards a pulsatile fatigue, correct?

MS. ABEL: Yes. So does the pulsatile test tell you anything about your hooks and barbs?

PARTICIPANT (Cook, Inc.): I think it depends on the test set up. We have test -- fatigue test which will test longitudinal fatigue as well.

MS. ABEL: So you incorporate longitudinal forces?

MR. SMITH: My experience, we've had to develop a separate test to specifically apply worse

case forces to anchors.

MR. RODGER: Yes, we also have developed a separate test.

MR. CARDELLA: Whether it's a separate test or not, I think it should be tested if that's the issue.

MS. ABEL: We're just talking about in this test. And so if you were to say that it should be evaluated in this test, obviously the test grammars would need to be modified so that you're adequately doing that. But if it needs to be evaluated in a separate test, we don't have to try to incorporate anything that would effect those hooks and barbs. Okay.

And this is where we're talking about the tearing, other failures of the fabric. It is mentioned in the ISO standard as something that you would be looking for. Only half the respondents were looking for it in their tests.

Is this a reasonable test to use to look at graft wear and tear and that sort of thing or are the conditions being, you know, inside of the mock

artery and just not simulating enough in terms of that particular failure mode?

Where's Frank? Frank, get to a microphone.

PARTICIPANT: I would say you don't use that test to determine that because you don't have the movement that is -- you should have a second test to determine friction between the two different components. You can get misled.

MS. ABEL: For those of you who don't know, Frank -- can I say it?

PARTICIPANT: Sure. Why not.

MS. ABEL: Worked on the Vangard project.

So I think it's certainly something that you would document if you did see an observation. But the test isn't specifically designed and adequate to look for that type of a problem?

PARTICIPANT: I think I would say again it depends on the design of your set up.

MS. ABEL: Yes. And you must have a respectable one that's different -- you should have

filled out your little homework and then maybe we could have --

PARTICIPANT: The dog ate it unfortunately,

DR. MARIN: Dorothy, I would add that I'm not clear exactly what you mean by other failures of the fabric. The fabrics, as you know, can restore before failure. And I guess where I think this test can be useful is identifying areas of distortion or movement of yarns that can create openings and so on that aren't necessarily failure points but suggest modificational changes in the structure during exposure to this type of durability test.

MS. ABEL: I think that's a very fair observation. But again, I think what we're saying is you need to design a separate test to look at, like you say, the changes in the fabric or the material. Tailoring it or wear or you know.

DR. MARIN: Distortion.

The point about fabrics is that they're usually, you know, the yarns are laying at the right

angle to each other and often under particularly nonuniform loading, you get distortion of the yarns -- no longer at right angles to others. So you can identify -- you can use the structure to identify places of stress concentration

MS. ABEL: Sure.

DR. MARIN: So I don't know if you want to add this to a specific others at the bottom. This is not particularly considered failure mode, but it is an observation of changes in the structure.

MS. ABEL: I think we'll just put it in with that and acknowledge again that that's something that should be observed in a test. Unfortunately, you can't really -- this test isn't designed to look at the -- or to challenge the fabric appropriately for the interaction of the fabric with the stent.

Okay. Detachment of the stent from the fabric. So the suture breaks. Is this the sort of test that helps you to identify that or do you need a separate one?

MR. WANINGER: I think that's a situation where you're going to document your observations, but I think you're going to want a separate test. At least in our experience we developed another one.

DR. MATSUMURA: I think when you're talking about that testing, too, it's important not just to test the device itself, but to test it after it's been loaded and the delivery system deployed in anatomy, you might expect, and then treat it sometimes by the physician in ways that you might not expect.

MS. ABEL: So you should bring in some physicians to deploy the devices in your testing in your marked arteries.

In the standard it does specify that the device should be manufactured and loaded and everything in accordance with the IFU and then deployed in accordance with the IFU.

DR. MATSUMURA: Well, just to emphasize the point that Rod and Tim made, on curved anatomy. I think the big thing that we miss on this

preclinical testing was on curved anatomy so when you deploy a graft encurved anatomy and then if you apply a balloon on the inside of that, that may do something different because it translates the load to one area of the graft radially as opposed to the whole circumstance which on curved anatomy is testing.

MS. ABEL: Yes. So we'll need to get into that when we talk about the specific modifications and things to consider in this test.

Migration, is this something that you can really look -- evaluate in this type of a test? I know you guys can evaluate everything. Anyone else, do you think you really can look for migration?

MR. SMITH: We did a very similar test but modified to make it worse case for potential migration.

MS. ABEL: So other than what we just talked about was pretty much you're looking for some sort of a fatigue or a fracture of the stent material or the attachment system, whatever you want

to call it. Is that really the only thing that you can look at in this test other than documenting observations?

Dan? Sorry. Okay. Jim. He's giving you the floor.

PARTICIPANT: Well, we have seen testing in the past that has shown --we have seen testing results in the past that have shown fabric abrasions similar to clinical results, the suture breaking and certain stent migration. I think a lot of it has to do with the protocols that one uses in their testing. And over the years we've made a lot of strides in the standards committees trying to focus in on that.

Sometimes we forget that the earlier data that's been prepared was not prepared with the most recent protocols.

And in those same meetings we have had statements from manufacturers who have indicated that there are protocols that do predict the number of cycles and the location of failure once those products go into the clinical setting.

So we need to remember that we're evolving in our testing and can't get stuck on the interpretation of all the data that seems to be unpredicted because there were certain protocol flaws associated with them.

MS. ABEL: Well, what's we're talking about right now is, like you say, the evolution. Should we be changing these tests so that we can better evaluate these different types of failure modes and what the majority of the people are saying, at least what I've heard so far, is that in one group because of the way that the tests are set up you aren't really capable of truly looking at whether you're going to have wear and abrasion. So it's interesting that --

PARTICIPANT: It's historical. I mean, that's true. That's historical information.

I think we have protocols at the various standards committees that we work on together that have addressed these issues. And it's possible that if the more modern protocols that we're coming up with we used throughout history, then we wouldn't

have so much of the concern and the unpredictability of the past testing.

MS. ABEL: Could some of the other folks who have been in the standards meetings respond?

PARTICIPANT (Medtronic): One of the things we discussed last time is that some of those things we cannot study because the grafts not pressurized. And also, there's a lot of nonphysiological graft material movement in that test at the accelerated testing speed.

So, just want to maybe ask the question whether the audience thinks that we should do something about trying to pressurize the graft from inside?

PARTICIPANT (Lombard Medical): We think it's a good idea to do that. We don't want to be too coy, but there are a number of really quite radical problems with traditional fatigue testing. And principally you tend to use superphysological pressures because you have to have to have a very stiff rubber tube in order to get the durability, which means that you get the correct movement but

the pressures and forces involved inside the stent graft tend to be different. Very often those sorts of models emit an aneurysm which is quite a major omission for a stent graft and of course are very difficult to put angulated necks in. And we've done that both to try to come up with a system which addresses those factors and is quite a bit more representative of the physiological situations. I would encourage people to move in that direction.

MS. ABEL: I know we're in the midst of a hot discussion here, but I think maybe we'd better take a break because I see quite a few are needing to get up, and I hate to be rude and not let Angie have a break, too. So if we can come back in ten minutes, we'll resume this discussion.

(Whereupon, at 10:21 a.m. a recess until 10:45 a.m.)

MS. ABEL: Welcome back, everybody.

I think if I remember right, you were standing there. Jim or Joe -- Jim, you're standing there.

We need to start with a little

announcement with respect to transportation.

MS. SMITH: I think the hotel actually had a sign-up sheet out on our registration table for those who need transportation from the hotel this afternoon or this evening. So if you do need transportation, sign up, I guess as soon as possible. Lunch, something like that. I think that's about it.

MS. ABEL: All right. Now that we have our housekeeping out of the way, Dan, do you remember what it was you wanted to say?

MR. CHWIRUT: I believe so.

Under the last row there specify others. I know you've got a totally separate section on corrosion, but I want to ask a question now is this test, the radial dilation pulsatile whole device durability test an appropriate way to test threading and galvanic corrosion for these devices if the appropriate environment is specified? So could they be put in as additional failure modes that can be assessed by this test? My opinion is yes.

MS. ABEL: The question that you missed,

Lou, whether corrosion could be a part of this test.

MR. SMITH: Threading and galvanic corrosion.

MR. CHWIRUT: If everybody agrees yes on this test, we can cross those off the discussion on corrosion.

MS. ABEL: Yes, right.

PARTICIPANT: I think it's still replicated to the test, corrosion.

MS. ABEL: Anyone else?

PARTICIPANT (Medtronic): I have a concern with respect to corrosion because this testing often induces non-physiological type of contact due to accelerated testing speed which may give you some artifacts.

DR. FOGARTY: We could slow the testing down.

MS. ABEL: Yes. Yes.

MR. SMITH: I think corrosion evaluations take combinations of tests, though. I mean, in this you can look at and say okay, yes, did I get any or whatever. But that's no different than

really flowing the metal in a bucket of saline for a certain amount of time, which was the old way of doing it. So, you know, just the interactions with the FDA and all other, and ASTM and all, there's been a proof toward this potential dynamic testing to kind of get a relative measure compared to other materials.

So I don't know -- even though you can look at it in this test, I don't know if the other types of evaluations go away.

MS. ABEL: So we'll get into that when we get to corrosion segment of the workshop. Thanks.

Jim, you had something else you wanted to say.

DR. CONTI: No, I'm okay.

MS. ABEL: You're okay now? Actually, he's not okay because he was asking me what it is we're trying to accomplish here. And I was saying what we're trying to figure out is, you know, exactly what does this test tell us now, are there things that we can do to make it tell us more or, you know, or do we just live with the fact that

there are different tests. And from what I've heard this morning, I think there are two ways of going about looking at what you need to look at. And I don't know that we know yet that when you come up with a more complicated model that our friends have done across the pond, whether that's going to give you all the information that you need. Because, you know, can you just tell us how much clinical experience you have, or you don't want to tell us?

PARTICIPANT: We have 36 cases implanted with a maximum plantation time of two years.

MS. ABEL: So you have at least some patients out longer term.

PARTICIPANT: Yes.

MS. ABEL: But a relatively small number of patients. So I guess, you know, time will tell if you've been able to predict. Although may you just have the best device in the world and it doesn't matter, you didn't even need to test it. I'm not sure the new test has been validated necessarily, but there are two ways of going about it. You can come up with new testing that

incorporates a lot of the things and, hopefully, you'll be willing to share with us again everything that you've incorporated into your tests or you can do the individual testing tests to look at the various aspects, the various failures that we're talking about.

PARTICIPANT: The other thing we've been doing is testing competitive devices and seeing how they check out in comparison with the clinical experiences.

MS. ABEL: Sure. So you'd better do that to validate your test.

And I had asked Jim if he wanted to tell us what he believes the state of the art is. You know, he said that he thinks that you can now evaluate things like wear and those sorts of things. And I just want to know why people sitting here don't think that you can look at fabric issues with the type of testing that we're talking about and Jim says that's possible, and he says that the test has evolved. And so I want to know what the evolutions are.

PARTICIPANT (Medtronic): I think one of the things why we cannot evaluate the wear at the present time is because of the extremely high testing speeds. So I think we should separate the metals from the fabric. And in metal fatigue in some development industries, you know, there are testing methodologies according to which you cannot -- you can test metals provided that you know the real service conditions. But however in fabric fatigue due to extremely accelerated speeds, you know, we can get a lot of artifacts because a lot of the nonphysiological graft material movement.

My experience is that we can better failure modes by slowing things down. Like fabric, usually one to hertz -- I can replicate the clinical failing ones. But at like 100 or 200 hertz, I don't think you can do that.

MS. ABEL: Okay. So it has to do with you're talking about different tests than what Dr. Chwirut uses?

Tom?

MR. GREENAN: Even the conduit material

could have very different results on fabric ware. So they're concerned about testing under these tests something that has the same displacement running at different speeds and running with different conduit material can have significantly different results. And I don't think we know how these may relate to the clinical conditions. Those are so me of the concerns.

MS. ABEL: Yes. Tom?

DR. FOGARTY: Yes. Part of the issue, I'm sure you would test for anything. But in reality, the points of stress and strain between the metal and the fabric continually changes as the aneurysm reconforms. So I don't know if it's possible to accommodate that in any testing because you don't know in what direction it's going to reconform. I mean, you can test all day in many, many cycles, but it really doesn't test what in fact happens in most patients.

MS. ABEL: Well, you're getting -- you know, it may not be predictive of exactly how the device is being challenged in a clinical situation.

But it certainly can give you some information.

I mean, we know that there's motion, so that if you test with motion, you can look at whether you've got some weak points. I mean, I would agree it's not -- I mean --

MR. GREENAN: Yes, no --

MS. ABEL: -- very clearly it's not going to tell you everything you need to k now.

MR. GREENAN: Yes. I agree with that. But if you interpolate that to you're going to prevent erosion or help prevent erosion, it may or may not.

DR. MARIN: Could I just clarify my understanding of what we're trying to measure here. Because let's be clear that bending fatigue is a very different phenomenon from abrasion. And so the test that you would design for measuring bending fatigue, for example, of the components whether it be the fabric or the stent components would be a separate test from looking at the surface abrasion between those two components. And bending fatigue, for example, you would want to look at a rate at

which you can accelerate the bending of the components and which would not necessarily be the same rate or the same displacement for the stent as for the fabric. Because their bending module is so very, very different. So that's one issue that is -- and, again, totally different from the question of ware. And surface ware and abrasion has to be taken as a separate issue where there is micromotion between the two surfaces moving against each other. And clearly that is a condition that one needs to try and reproduce, but does require control both of the area of contact and the pressure between the two as well as the speed and frequency of the cycling.

So yet there are very specific issues here and one ware fatigue, abrasion test will not do it all.

MS. ABEL: Right. Agreed.

Okay. Jim, did you want to talk about some of the improvements in the methodology over time?

DR.CONTI: Over the past several years two different groups have convened experts from

around the world to evaluate possible modifications to the durability testing done on stents and stent grafts. One is an ASTM committee and one is the AIME that reports to -- or represents us as a nation for the ISO.

MS. ABEL: It's actually the ISO Committee.

DR. CONTI: A lot of work has been done, hundreds and hundreds of hours of just committee alone, to say nothing of what's on the outside. But to summarize where we have come, we're trying to be sensitive to developing a replicate system that exposes the implantables to the kinds of chemistry and mechanical loading that they'll experience in vivo. In addition, we're trying to be sensitive to the fact that we need to generate enough information to predict safety of these products without burdening all of us that do testing with the enormously long lead times in the testing areas. We've been very sensitive to that.

How can we do the best testing that we can and do it in as quick a time as possible?

Now the things that we've agreed upon. I don't necessarily agree upon all the issues, but I'm pretty happy with in general where we've ended up. And it's really a very logical approach.

If you take a material, if you take what we call a mock vessel that has the appropriate biologically relevant properties and you put your product inside of that vessel and expose it to pulsatile loading, and you monitor with whatever techniques you can; high speed photography, an array of sensors, whatever it is that you're an expert at or have available and you determine the kind of motions that that vessel is applying to that product, then you are free to go ahead and test that faster and faster as long as you can verify that all the things that you saw at biologically relevant frequencies are being replicated at the higher frequencies. And that's within the general guidelines I think is a lot of ability for individual scientists and engineers to perhaps be a little bit creative, simply they have to validate what they're doing. But that's really the idea.

We don't just ahead and limit testing frequency just because we are philosophically against it and we don't go wild with the testing frequency. We use some rational measuring points to determine how fast can we test.

Now, in general there's a lot of pressure on all of us to try and test a little bit faster. We try to encourage individuals to try and test early and test often. Because if you get into a development project and you need to have something on the table in a year, and it's going to take you 14 months to test, well you're just under a terrible pressure situation. Earlier testing will help a lot to pick out things.

And in the data that you presented this morning I find one of the most encouraging things I've seen in a long time, and that is that we might be able to do a pretty good job deciding whether or not we go to the next step with the design based upon 36 months worth of testing, maybe 48 months worth of testing. A lot of stuff goes bad in that short period of time.

MS. ABEL: I'd be careful to make that assumption, because this is obviously just information that was pulled together. We don't know how many patients were out further. It may be that there are more failures going on, but certainly there are observations in the relatively shorter term.

DR. CONTI: Yes. And I think if it's true, it's very exciting because now that will give everyone -- everyone wants to do the best job they possibly can. And nobody wants to design, sell a bad medical product, particularly one that's so critically important to life. But if we can, you know, perhaps make certain judgments about things within a couple years worth of testing, then everybody can relax a little bit and maybe slow their testing down some and end up with more informative test results than we've gotten in general in the past.

So it's sort of where we've come after all these years.

MS. ABEL: Thank you.

So I think we've heard some of the problems with respect to trying to evaluate the additional failure modes is that people do the faster accelerated testing. And so there are different ways you can possibly address the problem. You can slow it down or you can do additional tests, or you can come with the more complicated model that lets you do everything in one single test. I can't wait to hear about it.

MS. WOODS: I have one more question. This is Terry Woods from the FDA.

I would just like know how many of you manufacturers think you get useful information of this test you're doing right now, this pulsatile fatigue test or are you just doing it because Dorothy and I saw you have to do it?

MS. ABEL: That a good question. Okay. How many think they get useful information? If you'll raise your hand? Get them up there, guys.

MR. SMITH: I think there's a lot of benefit in the tests. I mean, even if it's not-- for instance just a general fatigue tests we're

talking about. Even if it doesn't specifically address, say, fabric wear, it is an observation that can be made. And then if you see an issue in this test, it should lead you to potentially other tests or resolution of the issue through whatever means.

Just my colleague from Medtronic talked about 100 to 200 hertz in terms of maybe too fast for fabricware, and that's true. But generally these tests are run, you know, in the 50/40/30 hertz range.

PARTICIPANT (Medtronic): I would just like to caution here that I think the results of this test are quite useful, but I do believe that we have to be careful how we interpret data that we got from that test. And that we have to be familiar with, you know, metal fatigue and the fabric fatigue and what that test can give us. And, like, you know if we tested the highly elevated testing conditions, constant temperature test, it may give us a wrong failure mode. So we have to know at what level we have to be and at what testing we have to be to attack certain failure modes.

MS. ABEL: That's fair.

PARTICIPANT: This is a fine test, and I wouldn't want to do away with it. But you have to be aware of the limitations of it and if you want to play around with the edges where these different components are going to fail, you have to stress those components in the worse case cardinal scenario. And unless you're extremely lucky, it is unlikely that this test that will stress the skeletal elements to its maximal conditions is also going to stress some of the components. So you also have to do some individually specific individual test for a particularly designed feature that maximally stresses that particular design feature.

MS. ABEL: Thank you.

Is there anyone in the room that's willing to talk about having designed a product, found out in the clinic that it broke? Did anyone try to retest it, see if they could duplicate the failures? Anything like that? Okay, we have a couple who will admit it. Will you talk about it?

MR. SMITH: I'll talk about. It goes to

thoracic experience, though, it's not abdominal experience. Still want to talk about it?

I think the one thing and a lot of the stuff you've down today shows how early days have under estimated the types of forces. I mean we're talking forces, forces, forces. But, you know, there's motion and then bending independent of how much force it takes to do that. And I think in our thoracic device we had longitudinally oriented wires to provide columnar strength for deployment and short term antimigration, basically. And over time those fractures -- those spines were seen to fracture in a small number of cases.

And I think the first step when you have such an incident is to understand why something like that is occurring and then immediately try to reproduce it. And in trying to reproduce it, that's where you end up developing other tests. Okay.

And I showed a picture of a bending fatigue test setup that we have. Specifically we've been using it for the thoracic device. And the goal of that test was to: (1) reproduce the fractures

that we've seen clinically in the mode that we would see clinically. Not some benchtop mode. But, you know, to replicate what the explants were. And I think then now we have a baseline to improve upon.

MS. ABEL: What I was curious about, you know, did you test it in your old testing system?

MR. SMITH: Okay. Yes. You know, this is where I think Dr. Conti's been talking about how fatigue testing it has improved. It depends on how far back you go, you know, to say whether it's improved or not. It's obviously improved from the early '90s.

In the types of forces that were causing these longitudinal spines to fracture are not generated in the pulsatile fatigue test in and of itself. They can do some longitudinal stresses, you have some pressure but there's not actual bending. You can try to incorporate it in there. You had to develop a completely different test to replicate the failure mode.

MS. ABEL: Right. So is there anyone that had failures, went back to do a pulsatile

fatigue test with different parameters and then could duplicate it? Testing the old design?

MR. DEHDASHTIAN: Well, we did that, Dorothy in the Life Generation I. We had experienced some fracture, went back and revisited the FEA analysis as well as the testing how come it did not predict. And we found out that there is a lot more loads and not uniform loading on the graft that really causes miscalculation from our end. Forced us to rigorously test the device again on the generation II was duplicating the fractures that essentially happened in the clinical environment.

MS. ABEL: And what was the change to your test to make it a more rigorous test?

MR. DEHDASHTIAN: Just additional forces. The test didn't essentially change per se even though we knew we need to induce not uniform load. We weren't able, that comes back to Terry's question. We were not able to duplicate, even though we know what we want to do, were unable to do it in the best testing. We just increased the loading and the displacement essentially. And --

MS. ABEL: Did you change the components in your mock artery or anything?

MR. DEHDASHTIAN: Yes.

MR. SMITH: I can speak to that a little bit, too. I think that when you do the test, I don't know, seven years ago you have certain assumptions and if you're going to make a new device or modify, you have new assumptions today based on all the information that we get in workshops like this and other meetings. And I think the way that the standard pulsatile fatigue test has evolved, at least in my mind is, you know there are some critical things when you're running that test to ensure you're still getting the diametric deflections that you set the test up for and ensure that your device is following the mock artery if that's what you're going to rely on to create those diametric deflections. And also determining, you know, from either your own clinical data or literature or whatever, what types of compliance you really should be using, what types of pressure pulse you really should be using. The literature says 5

to 7 percent on triple A compliance. It's generally accepted in the ISO standard. We've written that down. But there's a whole range of pulse pressure that goes with that.

And you know, it's one thing to assume 120 over 80, it's another to assume 160 over 80. And then it's another to look at these patients and determine, gees, those with low compliance generally have high delta ps, and those with high compliance in their aorta tend to have low delta p issues. I mean, that's something that we've discovered out of this.

So how these tests have evolved in my mind is not necessarily by the equipment or the mock artery, but all the finer details. Okay. How do I make sure my graft is still following that mock artery? How do I make sure that I'm still getting the pressure pulse and the diameter deflections that I thought I had at day one at, you know, at the single aided 100, 200, 300 or 400 million cycle points. So that's how the test has evolved.

And in doing so, you know, you put in

the whole device instead of pieces and components and you can see the interaction. I think that's real important.

MR. DEHDASHTIAN: I think in continuation of what Lou said, the current test or the tests that we did may not duplicate the clinical. But what helped us, it's kind of evolving. It teaches us, it takes us to the next step -- it's like a stepping stone. Teaches us to go to the next step.

MS. ABEL: Medtronic, did you have something you wanted to say?

PARTICIPANT (Medtronic): No.

MS. ABEL: You had your hands up earlier.

MR. VASUTEK: And following on from Dr. Chuter's beautiful picture, it's quite clear that the motions change over the course of the implant as well. I think that's something that should be considered -- might be that you consider oversizing at worse case for the full duration of ten years or whatever. But it may be that the stent itself is

going to expand both in the mock artery and in the patient. So you may have a different boundary condition from the start of the test until the end of the test.

MS. ABEL: All right. Well, I think we're ready to move on to our next table then. So considering I think what I'd like to do here, I think what we talked about as far as pulsatile fatigue testing, the way that it's done by most people right now, we're really looking at primary the stent fracture of the stent fatigue. So if we think just with respect to that, are there other characteristics that should be incorporated within this testing to make sure that we've got as rigorous a test as possible to evaluate that parameter. And you can see that the majority of the people that responded to our survey said that they used straight devices, they didn't use bifurcated devices in their fatigue testing.

Is it we're at the point now where all these devices should be tested in a bifurcated system? Does that give you more information?

PARTICIPANT (Cook, Inc.): It gives you more information. On the mathematical calculations and in the test model we know that the strength comes on the stent immediately above the bifurcation. That's why it fractures there. And it also depends on the angle which strut will break.

So, but whether it makes any difference, I'm not sure other then that the broken strut can penetrate the fabric. But it's certainly a stress point. And it's a stress point that you would only see in the bifurcated model.

MS. ABEL: Yes.

DR. CONTI: I agree completely. I think the shape of the vessel that you put the device into has a huge amount of influence on where loading points actually occur. And if we're aware of certain risky scenarios in the shape of the recipient vessel, then we should try and in corporate that into the more quality of the mock vessel, because it does make a very big difference.

MS. ABEL: Thank you.

Robert?

DR. WHIRLEY: I think I very much agree that the important underlying premise is to identify and test whatever is worse case for a particular device. And in some cases that may well be in a bifurcated configuration. But I wouldn't want to see us move to mandating a bifurcated configuration if that required us to compromise on some other test parameters which could no longer be as challenging as they would be, say, in a bent tube configuration that might have a lot more angulation.

So I think the question may be a little more complex than just straight versus bifurcated.

MS. ABEL: So for the basic tests that people are doing right now, though, you know if you didn't incorporate any sort of a curvature or whatever, certainly bifurcated makes sense? I think your point's well take, though, if you make other changes.

PARTICIPANT (Cook, Inc.): I think they're different. I think that the stress on a curve is on the center of the curve. And the stress on a bifurcated system everything is different. So

it depends what graft you're testing. If you're testing a bifurcated graft, then you test that. And if it's a straight curve graft, you test that. Even if it's a tube curved graft.

MS. ABEL: Right. I guess what I understood, and maybe I misunderstood you, Robert, but I thought you meant that, you know, it could be that what you really want to look at is the curved vessel and to do that in a bifurcated model may be not possible or it may make your results difficult to interpret, or something.

DR. WHIRLEY: That's right. My point was just I would caution us from thinking that because it's a bifurcated model well everything is good and we've automatically incorporate the worst case configuration, whereas a worse case configuration might could be replicated in a much more complex angulated test setup but in a straight tube. And I think that has to be evaluated on a case-by-case basis to come up with what's worse case.

MS. ABEL: Mark?

DR. FILLINGER: I was pretty much going to say the same thing. I think guess the only thing I would sort of add to reinforce that is that when we're sort of setting IFUs for a certain degree of angulation and other sorts of things for the device, that the testing should be sort of directed to that. So you've got a bifurcated graft, you should test the bifurcated graft because if you say the IFU is going to have a certain degree of angulation allowable, the you should try and incorporate in your testing something that will replicate the stresses that would be induced by that degree of angulation.

MS. ABEL: Now is that something you can do in this test or is that something for a separate test to work out the angulation? What do people think about that?

DR. WHIRLEY: I think you could do it in this test. I think it depends on what you're looking at. If you're looking at the effect of angulation on dilatational fatigue, then you can probably do that in this test. But if you're looking at the

effect of angulation on longitudinal fatigue or some of the other aspects that we talked about this morning, that may well be better addressed in a different test.

MS. ABEL: And so what's most critical to address in this? I mean, you know, would you have value added by incorporating angulated mock artery or a --

MR. SMITH: I can say from experience it's somewhat difficult in this standard test setup to put in a certain type of angulation and still try to maintain everything else, especially when you're deciding what type of mock artery to use.

So, you know, yes it can be done because that's what engineers say they can do. But actually making that happen is a different thing.

In terms of what Dr. Fillinger said, which is pretty good, you can come up with ways to determine what the stresses are due to angulation and try to replicate them in different ways, either by more compression or more deflection or other things to say, okay, if I do see these additional

stresses, although it's not the exact type of thing that would happen with the material, it can happen easily with the metallic components and therefore you can say, okay, if I test at a higher stress even mean or alternating stresses, do I see more fractures. And then how does that relate to the stresses caused by angulation.

MS. ABEL: So I guess, you know, if we just look at this list here are there any characteristics that should be incorporated in the standard fatigue tests or should we leave that test alone and just note that other tests should be designed to evaluate these failure or these characteristics, or the effects of these characteristics?

DR. WHITE: From the clinical data that we've got, two, three, four year stuff there is a pattern in the devices where you can predict where the fractures are. And it distributed, at least as far as I've seen, predictably in each device. So why not model for that device or what we know from that two or three year data and forget all this term

stuff with bifurcations and 400 million cycle stuff which hasn't been predictive? I mean, I think you can refine the testing to the clinical scenario that we know exists rather than what's turned out to be a theoretical that didn't predict it.

MS. ABEL: Well, I don't know that you can say it didn't predict, because we don't know about the devices that have failed the test and having then gone on to be developed. So you don't know. I mean, it could have shown exactly what it should have shown.

DR. WHITE: And I understand that. But it didn't predict in the devices that are clinically used that failure mode.

MS. ABEL: But that doesn't mean that you should not do this test?

DR. WHITE: Yes, it does to m e.

MS. ABEL: Because what I'm saying is there may have been ten devices. People were developing devices, they did test and they saw fractures and so then they never went on to develop them or they modified their devices. And then they

retested, they didn't have the fractures --

DR. WHITE: But there's an assumption in there that that test meant something to start with in this area, which it doesn't. It came from stent technology transferred to this field and it turns out, it doesn't predict anything.

MS. ABEL: Actually, it was more graft testing I would say it evolved from.

DR. WHITE: Well, okay, that's right. Yes, conventional vascular grafts for stent technologies which in this case in a straight tube 400 million cycle ten year thing isn't predicting anything. And it's not predicting --

MS. ABEL: How can you say it doesn't predict anything if you've not seen the test results from everyone?

DR. WHITE: I think we have seen the test results from everybody.

MS. ABEL: Do you think everyone tells you all their testing and all their --

DR. WHITE: Well, what they tell you is published in public record. I mean, I don't --